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Title: Cost-effectiveness of panel tests for multiple pharmacogenes associated with adverse drug reactions: An evaluation framework

Running head: Cost effectiveness of a pharmacogenetic panel

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ABSTRACT

The cost-effectiveness of testing for multiple genes implicated in adverse drug reactions requires the simultaneous assessment of all actionable information, including future prescribing decisions based on incidental findings. We developed methodology for determining the value of pharmacogenetic panel tests, illustrated with a multi-gene panel including *HLA-A*31:01*, *HLA-B*15:02*, *HLA-B*57:01*, *HLA-B*58:01*, *HLA-B (158T)* and *HLA-DQB1 (126Q)*. If the findings for all alleles are acted upon, regardless of their individual cost-effectiveness, the HLA panel resulted in cost savings of £378 (US\$491), and a QALY gain of 0.0069. Based on a stratified analysis and compared with no testing, initial use of the panel was cost-effective in patients eligible for abacavir (*HLA-B*57:01*), carbamazepine (*HLA-A*31:01*) and clozapine (*HLA-B (158T)* and *HLA-DQB1 (126Q)*) but not for carbamazepine (*HLA-B*15:02*) or allopurinol (*HLA-B*58:01*). The methods presented allow for the assessment of the cost-effectiveness of multiple-gene panels.

INTRODUCTION

Pharmacogenomic-based personalised medicine holds the promise of optimising prescribing decisions by improving the targeting of treatment or reducing the likelihood of adverse drug reactions (ADRs), which are among the leading causes of iatrogenic morbidity and mortality [1]. In this context, genotyping can be used predictively in order to prevent ADRs by taking precautionary action such as excluding certain drugs, reducing the dose, or by providing increased monitoring to high-risk groups [2]. Pharmacogenetic information may also be used pre-emptively, that is, to inform a current prescribing decision based on stored data from previous genetic testing [3]; to inform practice for monitoring, and to assist with clinical diagnosis following a suspected ADR [2].

More than 10% of drug labels in the USA and EU contain information on genetic factors determining drug response, although only a minority of these have been implemented in current practice. This is mainly because of a lack of evidence on the clinical effectiveness and utility of testing, but also because of potential concerns about their cost-effectiveness [4]. As few as one in ten drugs with FDA labels which include genetic information have associated economic data [5], and of these only a minority are considered to be cost effective [6, 7]. The need for economic evidence will become more pressing, given the risk of the rapid pace of knowledge and technological advancements in genomics resulting in untested innovations being adopted as routine without evidence of cost-effectiveness [8].

It is acknowledged that the health technology assessment of diagnostic and prognostic tests is complex, but analytical frameworks have been developed [9]. Methods for assessing the cost-effectiveness of single-gene pharmacogenetic tests are well described [7, 10, 11], as are the challenges, which often include a lack of robust data, uncertainties around downstream costs and benefits, and the sensitivity of the results to key modelling assumptions [12, 13]. The advent of multi-gene panel testing and whole genome sequencing will require that multiple genes are assessed simultaneously, greatly enhancing the usefulness of testing, but also further increasing the complexity of assessing value.

Conceptually, a cost-effectiveness analysis of a multi-gene panel would necessitate a separate economic analysis of every informative result, each weighted to determine the overall cost-effectiveness. However, this poses significant challenges in terms of data requirements, modelling complexity and analytical approach. Assessing the value of a panel of pharmacogenes linked to ADRs to treatments for HIV, diabetes, hypertension and asthma, for instance, would become infeasible given the requirement to model the costs and outcomes for each disease. Some commentators have proposed a welfarist approach to the economic evaluation of genetic testing [14], given that

difficult-to-quantify benefits may be derived from predictive, diagnostic or prognostic information as well as potential improvements in health.

Many applications of next-generation sequencing panels consider a single disease such as a particular cancer, focus on diagnosis and risk to family members [15, 16], or guided treatment [15, 17], where models and outcomes focus on a single decision at a single point in time. Newborn screening panels consider a wider range conditions, but economic analyses often focus on the most prevalent or life-limiting outcome [18]. A review of cost-effectiveness of whole genome sequencing and whole exome sequencing noted that there were very few full economic evaluations, and indeed there was a paucity of robust evidence to inform economic evaluations [19]. A single study has been identified which considers the cost-effectiveness of pharmacogenetic panel testing, using a discrete event simulation model [20]. While this approach offers a flexible solution to assessing the cost-effectiveness of a small genetic panel test, it is not readily extensible to larger panels due to computational complexity and extensive data requirements.

The present study aims to formalise an alternative framework for assessing the cost-effectiveness of pharmacogenetic tests used in different clinical contexts of ADR management; and to introduce methodology for the efficient determination of the cost-effectiveness of a panel of multiple genes associated with ADRs.

RESULTS

Cost-effectiveness of a pre-specified 2-gene panel

A scenario of sequential testing, where a patient with epilepsy and eligible for carbamazepine is tested for *HLA-A*31:01* and who later develops gout and is eligible for allopurinol (and tested for *HLA-B*58:01*) is presented in Figure 1a. Compared with the standard practice of not testing, the reported incremental, total cost of genotyping for *HLA-A*31:01* alone is £300, inclusive of a test cost of £54 [21]. The incremental cost excluding the cost of testing (δCost) is £268 once inflated to 2017 GBP [22], and the incremental quality-adjusted life year (QALY) is 0.0234 [21]. Following the same approach for *HLA-B*58:01*, the incremental cost, excluding that of the test, is £49, and incremental QALYs 0.0023 [23]. Gout has an estimated incidence of 1.77 per 1000 person-years, with 27.3% of patients receiving urate lowering therapy within 12 months of diagnosis [24]. Of these, 89% are anticipated to receive allopurinol [25], resulting in 0.43 incident prescriptions of allopurinol per 1000 person-years.

Assuming each test costs £50 (US\$65), the incremental costs and QALYs of testing for both genes sequentially are £319 and 0.0234, respectively, resulting in an ICER of £13,611 (US\$17,695) per QALY gained (Box 1).

Box 1: Incremental cost and QALY of sequential testing for *HLA-A*31:01* and *HLA-B*58:01*

Based on Equation 1 $\Delta\text{Cost}_{A*31:01 \text{ Sequence}} = (£50 + £268) + 0.00043 * (£50 + £49) = £319$

Based on Equation 2 $\Delta\text{QALY}_{A*31:01 \text{ Sequence}} = 0.0234 + 0.00043 * 0.0023 = 0.0234$

Based on Equation 3 $\text{ICER}_{A*31:01 \text{ Sequence}} = £319 / 0.0234 = £13,611 \text{ per QALY gained}$

The inclusion of both genes in a single panel benefits from generating incidental findings at zero marginal cost. Box 2 presents a panel result depending on presenting condition, where results of incidental findings are considered exclusive of test cost (Figure 1b). Based on a panel test cost of £50, the incremental cost of testing for *HLA-A*31:01* inclusive of incidental findings for *HLA-B*58:01* is £318, and with a corresponding incremental QALY of 0.0234, resulting in an ICER of £13,610 (US\$17,694) per QALY gained. The reverse sequence, with *HLA-A*31:01* as an incidental finding, is estimated to cost £99 and generate 0.0023 additional QALYs, resulting in an ICER of £43,205 (US\$56,167) per QALY gained. This is based on 0.08 incident carbamazepine prescriptions per 1000 person-years, derived from the incidence of epilepsy, estimated at 0.51 per 1000 population per year [26], and the proportion of patients estimated to be prescribed carbamazepine (10%-20%) [Personal communication, Prof AG Marson, 26th February 2018, Dr G Powell 27th February 2018].

Box 2: Incremental cost and QALY of testing inclusive of incidental findings

Based on Equation 4: $\Delta\text{Cost}^+_{A*31:01} = £50 + £268 + 0.00043 * £49 = £318$

$\Delta\text{Cost}^+_{B*58:01} = £50 + £49 + 0.00008 * £268 = £99$

Based on Equation 5: $\Delta\text{QALY}^+_{A*31:01} = 0.0234 + 0.00043 * 0.0023 = 0.0234$

$\Delta\text{QALY}^+_{B*58:01} = 0.0023 + 0.00008 * 0.0234 = 0.0023$

Based on Equation 6: $\text{ICER}^+_{A*31:01} = £318 / 0.0234 = £13,610 \text{ per QALY gained}$

$\text{ICER}^+_{B*58:01} = £99 / 0.0023 = £43,205 \text{ per QALY gained}$

The cost-effectiveness of the panel, independent of presenting condition (Figure 1c), is calculated by weighting incremental costs and QALYs by the likelihood of testing for each allele which can be estimated from the relative proportions of incident allopurinol and carbamazepine prescriptions (Box 3). The contribution of *HLA-A*31:01* as the predictive test is calculated as 15% of predictive

tests, and the contribution of *HLA-B*58:01* is 85% of predictive tests. Overall costs and QALYs of the panel, compared with standard care of no testing are £133 and 0.0055, respectively, resulting in a panel ICER of £24,148 (US\$31,393) per QALY gained.

Box 3: Incremental cost and QALY of panel testing

Based on Equation 7: $\text{Weight}_{\text{carbamazepine}} = 0.00008 / (0.00008 + 0.00043) = 0.15$

$\text{Weight}_{\text{allopurinol}} = 0.00043 / (0.00008 + 0.00043) = 0.85$

Based on Equation 8: $\Delta\text{Cost}_{\text{Panel}} = 0.15 * £318 + 0.85 * £99 = £133$

Based on Equation 9: $\Delta\text{QALY}_{\text{Panel}} = 0.15 * 0.0023 + 0.85 * 0.0234 = 0.0055$

Based on Equation 10: $\text{ICER}_{\text{Panel}} = £133 / 0.0055 = £24,148 \text{ per QALY gained}$

Whilst on average, the overall panel cost effectiveness of £24,148 per QALY gained is acceptable at a threshold of £30,000 per QALY, testing predictively when a patient presents with gout is not cost-effective. However, acting on information on *HLA-B*58:01* is cost-effective as an incidental finding of a panel ordered for patients eligible for carbamazepine ($\delta\text{Cost} / \Delta\text{QALY} = £21,491$ (US\$27,938) per QALY gained). The optimised use of the panel costs £13,610 (US\$17,694) per QALY gained, equal to that of testing for *HLA-A*31:01*, inclusive of incidental findings. The improvement in cost-effective compared with sequential testing is enhanced when considering multiple genes.

Cost-effectiveness of a specified multi-gene HLA panel

The cost effectiveness of a £50 multi-gene panel for *HLA-A*31:01*, *HLA-B*15:02*, *HLA-B*57:01*, *HLA-B*58:01*, *HLA-B (158T)* and *HLA-DQB1 (126Q)*, dependent on the initial predictive test, is presented in Table 1. For a patient with epilepsy and eligible for carbamazepine or phenytoin (with the incidental findings for all other HLA-alleles), the panel had an ICER of £15,638 (US\$20,330) per QALY gained and would be considered cost-effective with a probability of 0.75 at a threshold of £30,000 per QALY. The panel would also be considered to be cost-effective for a patient with HIV eligible for abacavir, or a patient with treatment-resistant schizophrenia eligible for clozapine, both at a probability of 1.0. However, based on a patient presenting with gout, an initial panel test request for *HLA-B*58:01* (with incidental findings for all other HLA-alleles) had an ICER of £43,038 (US\$55,950) per QALY gained, and a probability of 0.26 of being cost-effective at £30,000 per QALY.

In the case that the panel was to be implemented such that all findings are acted upon (where applicable) regardless of cost-effectiveness, the panel resulted in a cost saving of £378 (US\$491) and 0.0069 QALYs gained, therefore dominating standard care (Table 2). The probability of cost-

effectiveness at the £30,000 per QALY threshold was 1.0 indicating that this panel configuration is cost-effective, and should be adopted into routine practice.

Cost-effectiveness of an optimized multi-gene panel

In the context of designing an optimal panel to maximise cost-effectiveness for the National Health Service (NHS) in the UK, testing for *HLA-B*15:02* is not cost-effective, even as an incidental find (incremental net monetary benefit, INMB -£36; -US\$47) and is consequently removed from the panel. Testing for *HLA-B*58:01* is only cost-effective as an incidental find, and is therefore not included as a predictive test within the overall panel result (INMB -£30; -US\$40). In this configuration, the panel results in a cost saving of £1,388 (US\$1,805) and a QALY gain of 0.0163.

Both the pre-specified and optimised panels are viable, (i.e. the probability of the panel being cost-effective for initial use in at least two conditions was 1.0) which in a policy context suggests multi-gene testing to be more appropriate than single-gene testing.

DISCUSSION

This study introduces methods for determining the economic value of panel-based genotyping to diagnose, predict, exclude, monitor and pre-empt adverse drug reactions. The case study illustrated how the cost-effectiveness of a panel depends critically on the cost-effectiveness of incidental findings, the likelihood of future exposure to other pharmacogenetic drugs, the context of the initial request for the test, as well as the effectiveness and downstream costs of testing. In the case of acting on the main or incidental findings of a £50 multi-gene panel test for *HLA-A*31:01*, *HLA-B*15:02*, *HLA-B*57:01*, *HLA-B*58:01*, *HLA-B (158T)* and *HLA-DQB1 (126Q)*, the panel is both cost saving and more effective, than standard care. However, cost-effectiveness can be further improved by removing *HLA-B*15:02*, and not using the panel as a predictive test in patients presenting with gout who are eligible for allopurinol.

The analysis is novel in that it allows for the assessment of cost utility of multi-gene testing in different contexts, across a variety of conditions, through all incidental findings. Veenstra, (2016) [27] proposed generalised estimates of incremental clinical benefit, derived by improving drug effectiveness or avoiding harm, and incremental costs saved (or spent) as a result of modifying drug therapy and avoiding adverse outcomes, in the context of warfarin pharmacogenetic screening. The analysis is limited by having no derivation of how these can be calculated more specifically – e.g. relating to positive predictive value (PPV), negative predictive value (NPV), cost or benefit of avoiding specific ADR; restricted to a 2-gene panel (*CYP2C9* and *VKOR* variants); considered immediately relevant information (and so no weighting for incidental findings); and defined incremental cost in terms of an overall screening panel, rather than on presentation of condition. A discrete event simulation model applied previously in the context of a multigene panel, is limited by computational requirements, which can restrict their applicability to a small number of risk genes [20]. Moreover, they do not overcome the problem of needing to model each and every disease impacted by the use of testing. Our frameworks for estimating the cost-effectiveness of single-gene tests, whilst simplified from a full model, have the strength of using lifetime data reflecting downstream costs and consequences.

There are a number of key assumptions, however, which also limit our analysis. We assume independence of conditions and allele prevalence and we assume that drug prescriptions are independent and that there is no cross-reactivity between drugs. These factors could conceivably be incorporated into the analysis, provided the necessary information is available for simulation. The case study may be limited by heterogeneity, in that the ICERs for each single gene test are conducted on disparate populations.

In conclusion, this study has presented methodology which can be used to assess the potential future costs and benefits of multi-gene panels. Whilst the specific context is prevention of adverse drug reactions, this framework may be adapted for economic evaluation of multi-gene panels for other applications.

METHODS

A framework for assessing the economic value of multi-gene panel testing was developed to estimate the cost-effectiveness of a pre-specified panel, assuming action upon test results for all future relevant prescription decisions; and to design a cost-effective panel through selection of appropriate genes for action predictively and within incidental findings (this is equivalent to specifying how best to utilise an existing panel). Both approaches are presented in the context of diagnosing, predicting, excluding, monitoring and pre-empting adverse drug reactions [2]. The methods are introduced by describing each step in relation to a 2-gene panel. A case study of a multi-gene panel test is then developed to illustrate the practical application of the methods.

To improve modelling efficiency, two analytic approaches are proposed: One based on evidence available from existing economic evaluations of single gene tests, and the other, for situations where such evidence does not exist, based on economic evaluations of the drugs causing the ADRs in question.

Estimating the cost-effectiveness of a pre-specified 2-gene panel

In the context of a single gene test, the incremental cost (ΔCost) is the sum of the test cost (Cost_{PGx}) and the cost of acting upon the results (such as in relation to prescribing alternative doses or medicines), (δCost). The incremental cost-effectiveness ratio is ΔCost divided by the incremental QALY (ΔQALY). If two single gene tests are used in sequence, the overall cost-effectiveness (versus a strategy of not testing) is a function of Cost_{PGx} , δCost and ΔQALYs associated with each test, and the likelihood of patients requiring the second test. Figure 1a presents a schematic representation of testing for *HLA-A*31:01* and *HLA-B*58:01* in sequence for predicting severe ADRs to carbamazepine and allopurinol, with calculations for cost-effectiveness of this scenario presented below.

$$\text{Equation 1} \quad \Delta\text{Cost}_{A*31:01 \text{ Sequence}} = (\text{Cost}_{\text{PGx}} + \delta\text{Cost}_{A*31:01}) + \text{Incidence}_{\text{allopurinol Rx}} * (\text{Cost}_{\text{PGx}} + \delta\text{Cost}_{B*58:01})$$

$$\text{Equation 2} \quad \Delta\text{QALY}_{A*31:01 \text{ Sequence}} = \Delta\text{QALY}_{A*31:01} + \text{Incidence}_{\text{allopurinol Rx}} * \Delta\text{QALY}_{B*58:01}$$

$$\text{Equation 3} \quad \text{ICER}_{A*31:01 \text{ Sequence}} = \Delta\text{Cost}_{A*31:01 \text{ Sequence}} / \Delta\text{QALY}_{A*31:01 \text{ Sequence}}$$

If both genes were included in a single panel, information on the second allele is incidental to the principal findings (Figure 1b). Assuming the panel unit cost includes all aspects of testing (including for instance, quality control, relevant aspects of clinical decision support systems and electronic health records), incidental findings are available at zero marginal cost. In this context, the incremental costs ($\Delta\text{Cost}^+_{A*31:01}$) and QALYs ($\Delta\text{QALY}^+_{A*31:01}$) of testing for *HLA-A*31:01* predictively, inclusive of incidental findings (denoted by $^+$) can be modelled according to:

$$\text{Equation 4} \quad \Delta\text{Cost}^+_{A*31:01} = \text{Cost}_{\text{Panel}} + \delta\text{Cost}_{A*31:01} + \text{Incidence}_{\text{allopurinol Rx}} * \delta\text{Cost}_{B*58:01}$$

$$\text{Equation 5} \quad \Delta\text{QALY}^+_{A*31:01} = \Delta\text{QALY}_{A*31:01} + \text{Incidence}_{\text{allopurinol Rx}} * \Delta\text{QALY}_{B*58:01}$$

$$\text{Equation 6} \quad \text{ICER}^+_{A*31:01} = \Delta\text{Cost}^+_{A*31:01} / \Delta\text{QALY}^+_{A*31:01}$$

For a patient who presents initially with gout, who later has a possibility of developing epilepsy, an ICER can similarly be derived for testing for *HLA-B*58:01* inclusive of incidental findings for *HLA-A*31:01* by substituting *HLA-A*31:01* for *HLA-B*58:01* in the above equations.

Costs and QALYs for the panel, independent of presenting condition, are a composite of both possible predictive tests, where the contribution of each starting point is based on the relative likelihood of testing for *HLA-A*31:01* before *HLA-B*58:01* (or *vice versa*):

$$\text{Equation 7} \quad \text{Weight}_{\text{carbamazepine}} = \text{Incidence}_{\text{carbamazepine Rx}} / (\text{Incidence}_{\text{carbamazepine Rx}} + \text{Incidence}_{\text{allopurinol Rx}})$$

$$\text{Equation 8} \quad \Delta\text{Cost}_{\text{Panel}} = \text{Weight}_{A*31:01} * \Delta\text{Cost}^+_{A*31:01} + \text{Weight}_{B*58:01} * \Delta\text{Cost}^+_{B*58:01}$$

$$\text{Equation 9} \quad \Delta\text{QALY}_{\text{Panel}} = \text{Weight}_{A*31:01} * \Delta\text{QALY}^+_{A*31:01} + \text{Weight}_{B*58:01} * \Delta\text{QALY}^+_{B*58:01}$$

$$\text{Equation 10} \quad \text{ICER}_{\text{Panel}} = \Delta\text{Cost}_{\text{Panel}} / \Delta\text{QALY}_{\text{Panel}}$$

Estimating the cost-effectiveness of a multi-gene HLA panel

The methods for extending and generalizing beyond a 2-gene panel, to a multi-gene panel, are presented in the Supplementary Appendix. These are illustrated with a more comprehensive HLA gene panel for preventing ADRs. Additional cost-utility analyses for *HLA-B*15:02* [28], *HLA-B*57:01* [29], and *HLA-B (158T)* and *HLA-DQB1 (126Q)* [30] were identified from a purposive search of the literature. In this illustrative example, we relaxed assumptions of cost perspective and healthcare setting.

The incremental cost (exclusive of the test cost, δCosts) associated with a strategy of testing compared with standard care, and associated differences in ΔQALYs were extracted for analysis. Costs were converted to GBP [31], and then inflated to 2017 values using the hospital and community health services index [22]. The main results are presented also in US dollars, using a currency exchange rate of \$1.30 to the pound.

All inputs into the economic model of the multi-gene panel are summarised in Table 3. Analyses were conducted based on a panel costing £50 to estimate the ICER of the panel by assuming all results are acted upon, where applicable; and in the context of designing a cost-effective panel, based on a cost-effectiveness threshold of £30,000 per QALY (λ) [35]. Parameter uncertainty was considered using Monte-Carlo simulation, drawing from the distributions of the input parameters, to

generate 95% central ranges (CR) for the incremental costs and QALYs, and to calculate the likelihood of each single gene test being included as a predictive test, or within the incidental findings.

Designing an optimized multi-gene panel

An efficient panel test can be designed by including tests for genes which are cost-effective individually (within incidental findings), or in combination (as a predictive test inclusive of incidental findings). This is achieved by imposing the following conditions:

- i) In order to exclude tests which are not cost-effective within the incidental findings, a threshold is applied on the INMB for incidental findings. Genes are only included on the panel if $INMB = \lambda * \Delta QALY - \delta Cost \geq 0$
- ii) In order to exclude tests which are not cost-effective predictively (inclusive of incidental findings), in the final panel calculations (Equations 5 and 6), only predictive tests where
- iii) A multi-gene test is then defined as being viable, over and above a single gene test, when there are at least two combinations of drug-allele and indication, for which $INMB^+ \geq 0$. Based on simulation, using a series of Monte Carlo replications, the likelihood of a test being viable is defined as the proportion of replications in which multiple $INMB^+ \geq 0$

Methods for approximating incremental costs and QALYs for single gene tests

Where published single gene economic evaluations cannot be identified, or cannot be practicably performed (e.g. because of the number and complexity of considering multiple genes or drugs), then approximation of cost-effectiveness is required. This concept has been discussed previously in terms of the costs saved and benefits gained through pharmacogenetic testing [27]. Here, we propose further methods to estimate values of $\Delta Cost$, $\delta Cost$, and $\Delta QALY$ using existing evidence on the costs and QALYs of both treatment, and the ADR avoided. These are dependent on the context of testing [2].

Predicting adverse drug reactions

Genotyping can be used predictively to inform a specific prescribing decision (pre-prescription genotyping). This might determine whether a patient is at an increased risk of experiencing an ADR, and provide information on whether an alternative drug is indicated or whether a dose reduction is warranted. Patients with the *HLA-B*57:01* allele, for instance, must avoid abacavir and be prescribed an alternative anti-retroviral drug for their HIV infection as they would otherwise be at 15-fold higher risk of experiencing a hypersensitivity reaction compared with the general population [36].

Information on variant *CYP2C9* or *VKORC1* alleles can be used to guide warfarin dose, to reduce the risk of haemorrhagic events, and maintain effective anticoagulation [37].

Assuming that there is an appropriate alternative treatment (or dose) that is associated with no risk of the same ADR, the incremental costs and QALYs of genotyping may be readily estimated. Most ADRs occur soon after treatment commencement, and so the consequences of their avoidance are captured by the short term cost savings and QALYs gained. As cost-effectiveness relies on incremental costs and QALYs, only differences between strategies, highlighted in Figure 2, are considered in the final derivation (see Supplementary Appendix).

For chronic treatments (Figure 2a), the long term costs and consequences (including harms) are captured in the incremental costs ($\Delta\text{Cost}_{\text{alternative}}$) and QALYs ($\Delta\text{QALY}_{\text{alternative}}$), relative to the alternative drug (or dose) indicated by the test result or prescribed for patients who experience an ADR. These can be derived from relevant published economic evaluations.

Based on these, the incremental costs of a single-gene test can be approximated by sum of the cost of testing; the incremental cost of the alternative weighted by the probability of being prescribed the alternative; less the cost of ADR avoided (weighted by the likelihood of ADR)

Equation 11:

$$\begin{aligned}\Delta\text{Cost} &= \text{Cost}_{\text{PGx}} \\ &+ P(\text{allele}) * (1 - \text{PPV}) * \Delta\text{Cost}_{\text{alternative}} \\ &- P(\text{allele}) * \text{PPV} * \text{Cost}_{\text{ADR}}\end{aligned}$$

and the corresponding incremental QALY, by the sum of the incremental QALY of the alternative weighted by the probability of being prescribed the alternative, and the QALYs gained through avoiding the ADR

Equation 12:

$$\begin{aligned}\Delta\text{QALY} &= P(\text{allele}) * (1 - \text{PPV}) * \Delta\text{QALY}_{\text{alternative}} \\ &- P(\text{allele}) * \text{PPV} * \text{QALY}_{\text{ADR}}\end{aligned}$$

where, $P(\text{allele})$ is the probability of the presence of the risk allele, and PPV is the positive predictive value of the test, that is, the probability of a patient experiencing the ADR if they test positive for the allele. Cost_{ADR} is the cost of treating the ADR, and QALY_{ADR} is a QALY decrement associated with the ADR.

For cases where there does not exist an alternative drug (or dose) with a negligible risk of the same ADR (Figure 2b), then incremental costs and QALYs of prescribing an alternative drug (where the ADR is not mediated by the same allele) can be calculated as:

Equation 13:

$$\begin{aligned} \Delta\text{Cost} &= \text{Cost}_{\text{PGx}} \\ &+ P(\text{allele}) * (1 - \text{PPV}) * \Delta\text{Cost}_{\text{alternative}} \\ &- P(\text{allele}) * (\text{PPV} + \text{PPV} * P(\text{ADR})_{\text{alternative}} - P(\text{ADR})_{\text{alternative}}) * \text{Cost}_{\text{ADR}} \end{aligned}$$

Equation 14:

$$\begin{aligned} \Delta\text{QALY} &= P(\text{allele}) * (1 - \text{PPV}) * \Delta\text{QALY}_{\text{alternative}} \\ &- P(\text{allele}) * (\text{PPV} + \text{PPV} * P(\text{ADR})_{\text{alternative}} - P(\text{ADR})_{\text{alternative}}) * \text{QALY}_{\text{ADR}} \end{aligned}$$

Costs and QALYs associated with a second ADR are considered additively; however it is assumed that in the event of an ADR with the alternative drug (or dose), then a further alternative has the same costs and QALYs as the alternative, but no further risk of ADR.

In cases where the ADR is associated with non-negligible mortality (Figure 2c),

Equation 15:

$$\begin{aligned} \Delta\text{Cost} &= \text{Cost}_{\text{PGx}} \\ &+ P(\text{allele}) * (1 - \text{PPV}) * \Delta\text{Cost}_{\text{alternative}} \\ &+ P(\text{allele}) * \text{PPV} * P(\text{mort}) * \text{Cost}_{\text{alternative}} \\ &- P(\text{allele}) * \text{PPV} * \text{Cost}_{\text{ADR}} \end{aligned}$$

Equation 16:

$$\begin{aligned} \Delta\text{QALY} &= P(\text{allele}) * (1 - \text{PPV}) * \Delta\text{QALY}_{\text{alternative}} \\ &+ P(\text{allele}) * \text{PPV} * P(\text{mort}) * \text{QALY}_{\text{alternative}} \\ &- P(\text{allele}) * \text{PPV} * \text{QALY}_{\text{ADR}} \end{aligned}$$

where, $\text{Cost}_{\text{alternative}}$ and $\text{QALY}_{\text{alternative}}$ are the costs and QALYs associated with using the alternative drug, and $P(\text{mort})$ is the probability of not surviving the ADR.

Treatments indicated for acute conditions require additional considerations (Figure 2d). Existing economic evaluations are likely to be limited in having a short time horizon, whereas patients might

be exposed to treatment (and risk of ADR) on any number of future occasions. In this case, the long term consequences of a change in regimen are multiplied by the anticipated future number of prescriptions of the drug over a patient's lifetime, N_{future} :

Equation 17:

$$\begin{aligned} \Delta\text{Cost} &= \text{Cost}_{\text{PGx}} \\ &+ P(\text{allele}) * (1 - \text{PPV}) * \Delta\text{Cost}_{\text{alternative}} * N_{\text{future}} \\ &- P(\text{allele}) * \text{PPV} * \text{Cost}_{\text{ADR}} \end{aligned}$$

Equation 18:

$$\begin{aligned} \Delta\text{QALY} &= P(\text{allele}) * (1 - \text{PPV}) * \Delta\text{QALY}_{\text{alternative}} * N_{\text{future}} \\ &- P(\text{allele}) * \text{PPV} * \text{QALY}_{\text{ADR}} \end{aligned}$$

Pre-empting adverse drug reactions

Once information on a patient's genotype is already known (either due to a panel test, whole genome sequence, or a prior single-gene test which is relevant to more than one drug), the information may be used to guide a patient's future drug therapy (incidental findings) [2]. As with the case of prediction, the information may be used to exclude a drug from the regimen of high risk patients, reduce the dose, or implement a risk-based adjustment of their monitoring programme.

Incremental costs (denoted as δCost) can be approximated in the same way as for the case of prediction, but with the omission of test cost, as this represents a sunk cost following the initial test.

Equation 19:

$$\delta\text{Cost} = \Delta\text{Cost} - \text{Cost}_{\text{PGx}}$$

The QALYs associated with pre-empting ADRs in this way, are calculated as for prediction.

Monitoring adverse drug reactions

Where there are no alternative treatments (such as for patients requiring clozapine for treatment-resistant schizophrenia, but who are also carriers of *HLA-DQB1*) [38], or where the genetic risk factor may predispose to both mild and serious ADRs (e.g. *HLA-A*31:01* and carbamazepine) [39], pharmacogenetic information may be used to implement a monitoring programme that stratifies patients based on their risk of ADR [2]. The monitoring of high risk patients may be more frequent or

intensive compared with that of low-risk patients, who may receive less monitoring and experience no increased risk of ADR.

The economic analysis of monitoring is not as straightforward as for prediction (Figure 2e), as the proportion of patients who change treatment may not be the same as the proportion of ADRs reduced, and the cost of monitoring may be attributed to a change in either or both high (increased monitoring) and low (decreased monitoring) risk patients. The model therefore applies adjustments (based on *a priori* assumptions) to the above formulae, based on the proportions of ADR reduction and regimen change as a result of monitoring.

Equation 20:

$$\begin{aligned}\Delta\text{Cost} &= \text{Cost}_{\text{PGx}} \\ &+ P(\text{allele}) * \text{Cost}_{\text{Monitor}} \\ &+ P(\text{allele}) * P(\text{regimen change}) * \Delta\text{Cost}_{\text{alternative}} \\ &- P(\text{allele}) * \text{PPV} * P(\text{ADR reduction}) * \text{Cost}_{\text{ADR}}\end{aligned}$$

Equation 21:

$$\begin{aligned}\Delta\text{QALY} &= P(\text{allele}) * P(\text{regimen change}) * \Delta\text{QALY}_{\text{alternative}} \\ &- P(\text{allele}) * \text{PPV} * P(\text{ADR reduction}) * \text{QALY}_{\text{ADR}}\end{aligned}$$

Diagnosis of adverse drug reactions

Diagnostic pharmacogenetic testing has clinical utility in distinguishing the cause of a disease (Figure 2f). For instance, if a patient with gallstones were to present with jaundice, but who was also taking flucloxacillin, a negative test for *HLA-B*57:01* could exclude flucloxacillin as being the cause of the jaundice [2, 40]. Without correct determination of causality, flucloxacillin might have been stopped inappropriately, and the patient would be noted as being allergic to flucloxacillin, and prescribed alternative (and potentially more expensive and less effective) antibiotics in the future. The downstream benefits of diagnostic pharmacogenetic testing would include avoidance of alternate antibiotics, reduced need for further diagnostic testing and potential impacts on antimicrobial resistance.

In the context of diagnosis and tests with high NPV, the presence of an allele would suggest the drug as the cause, and the patient would be prescribed alternatives in future. A negative test result would exclude the drug as being the cause of the symptoms, and the patient may continue their prescribed medication. In standard care, further diagnostic testing may be required to establish causality.

The incremental costs of using genetic testing for diagnosis can be approximated as:

Equation 22:

$$\begin{aligned}\Delta\text{Cost} &= \text{Cost}_{\text{PGx}} \\ &\quad - (1 - P(\text{allele})) * \Delta\text{Cost}_{\text{alternative}} * N_{\text{future}} \\ &\quad - P(\text{allele}) * \text{Cost}_{\text{diagnosis}}\end{aligned}$$

The corresponding incremental QALYs can be approximated as:

Equation 23:

$$\begin{aligned}\Delta\text{QALY} &= -(1 - P(\text{allele})) * \Delta\text{QALY}_{\text{alternative}} * N_{\text{future}}\end{aligned}$$

STUDY HIGHLIGHTS

What is the current knowledge on the topic?

Demonstration of cost-effectiveness is a barrier to the broader adoption and implementation of pharmacogenetic testing in routine practice.

What question did the study address?

How can the cost-effectiveness of multi-gene panels for avoiding adverse drug reactions be assessed, and how can a cost-effective panel be designed?

What does this study add to our knowledge?

Methods are developed which allow for the cost-effectiveness assessment of multi-gene panels, and which consider the multitude of affected drugs, clinical indications and prescribing decisions. This is illustrated with a case study of a multi-gene HLA panel.

How might this change clinical pharmacology or translational science?

As multi-gene panel testing and whole genome sequencing become credible alternatives to single gene tests, assessment of their cost-effectiveness is particularly relevant given that the availability of additional genetic information could impact on any number of future prescribing decisions.

AUTHOR CONTRIBUTIONS

MP, DH conceived the study and acquired funding. All authors were involved in the study design. CP & DH collected the data, developed the methods of analysis and, together with MP, interpreted the findings. CP drafted the manuscript, and all authors revised it for intellectual content and approved it for publication.

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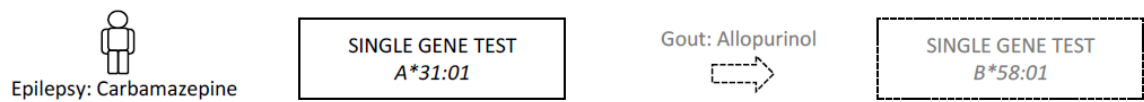
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(a) Single gene tests



(b) Panel use dependent on presenting condition

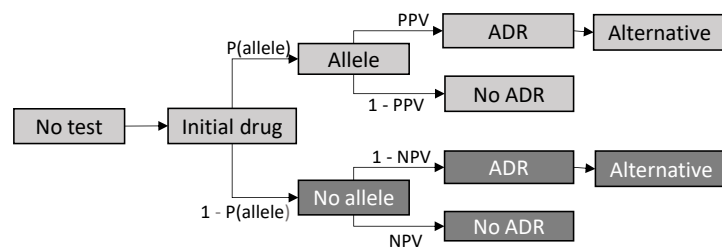
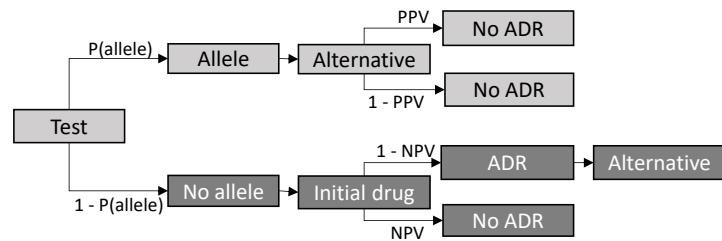


(c) Panel use independent of presenting condition



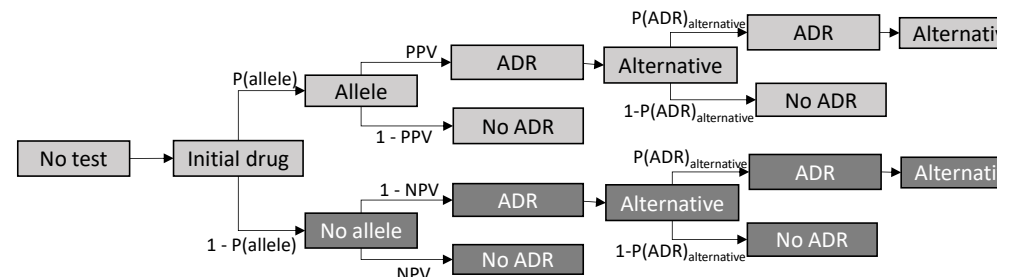
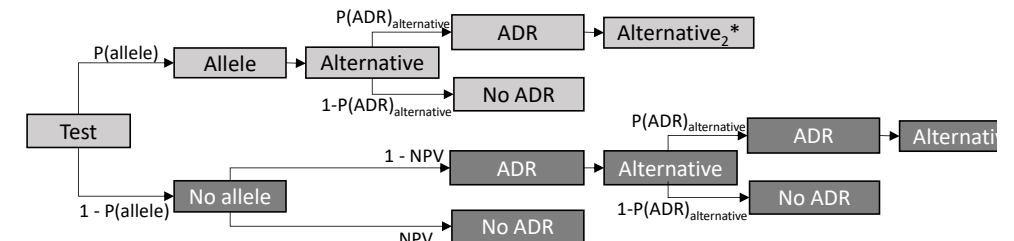
Figure 1: Illustration of (a) single gene testing, including the option of sequential testing; (b) incidental findings; and (c) panel testing for the 2-gene case study.

A

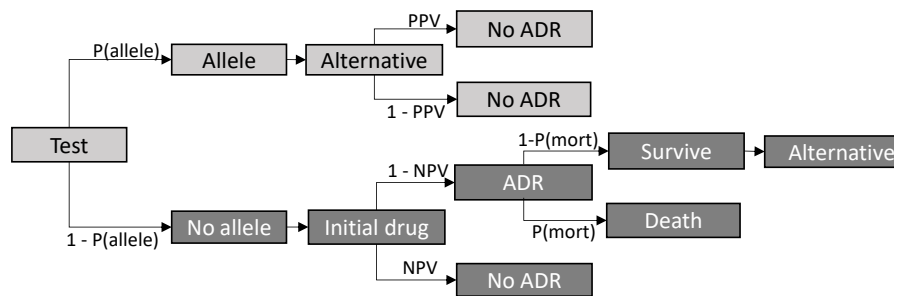


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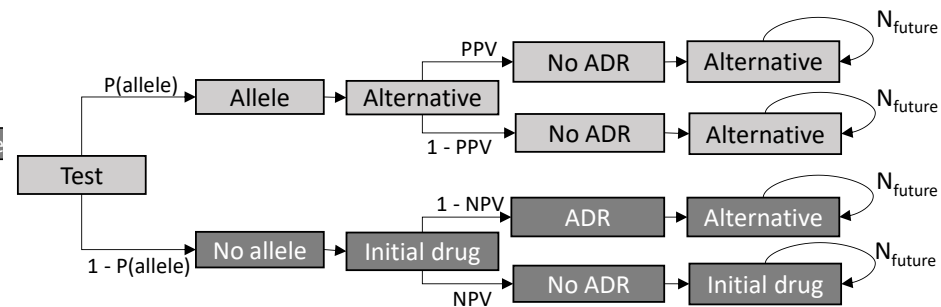
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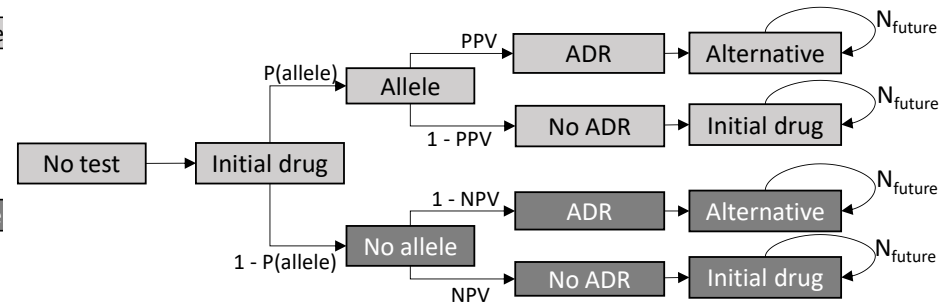
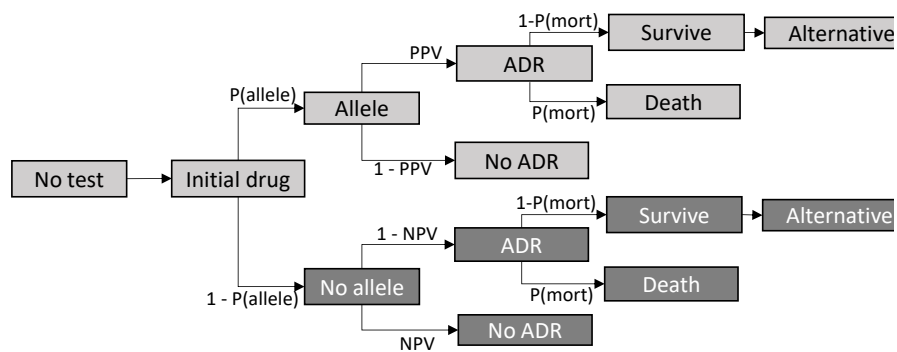
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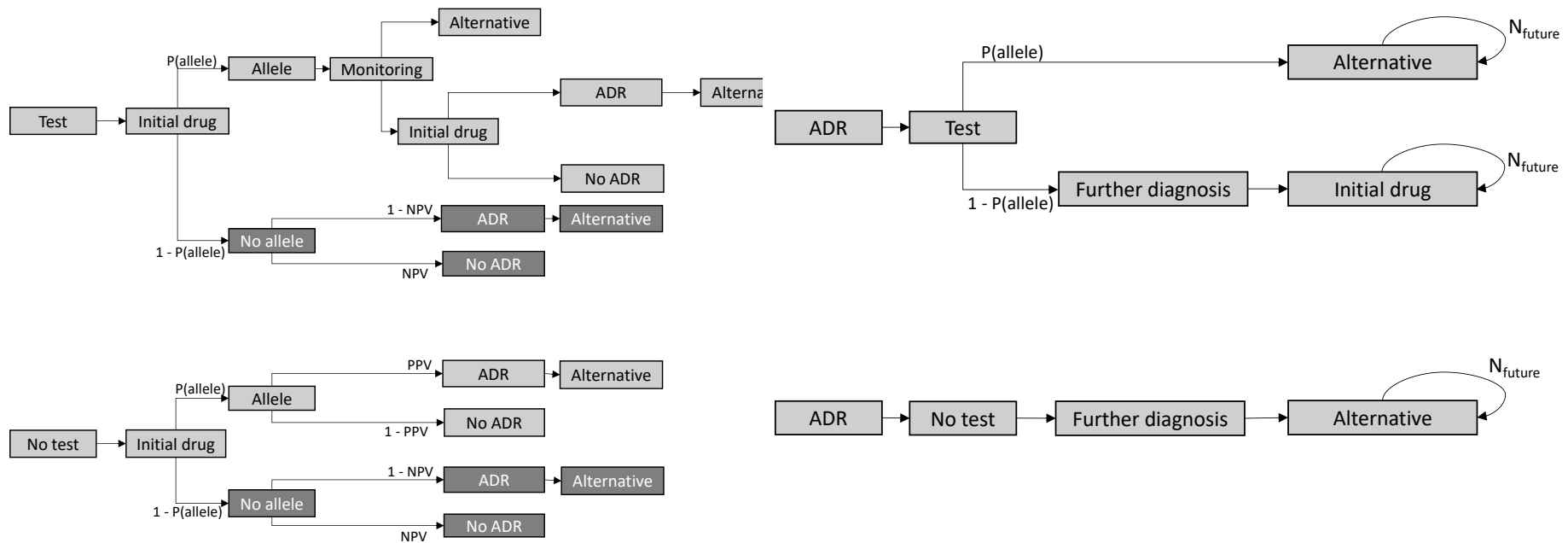


Figure 2: Schematic representation of decision trees illustrating (a) the use of an alternative treatment (or dose) associated with no ADR; (b) the use of an alternative treatment (or dose) which is associated with an ADR that is not mediated by the same allele; (c) the incorporation of mortality effects associated with the ADR; (d) the use of testing in the context of acute treatments; (e) the use of testing where change in monitoring is warranted; and (f) the use of pharmacogenetic testing for diagnostic purposes.

In incremental analysis, between strategies of testing and not testing, the darker shaded branches of the decision trees cancel.

NPV: Negative Predictive Value; PPV: Positive Predictive Value; P: probability; ADR: Adverse Drug Reaction

*Pragmatically, Alternative₂ assumed to have same costs and QALYs as first alternative, but zero risk of ADR

Table 1: Multi-gene panel test result, dependent on presenting indication

Allele Drug Condition	Cost-effectiveness of single gene test costing £0 (incidental finding)	Cost-effectiveness of single gene test costing £50	Cost-effectiveness of pre-specified panel costing £50 (by presenting condition)	Cost-effectiveness of optimised panel costing £50 (by presenting condition)
<i>HLA-A*31:01</i> Carbamazepine Epilepsy	1. £268 2. 0.0234 3. £11,473/QALY 4. INMB: £434 5. 80%	1. £318 2. 0.0234 3. £13,610/QALY 4. INMB: £384	1. £378 2. 0.0242 3. £15,638/QALY 4. INMB: £348 5. 75%	1. £318 2. 0.0234 3. £13,596/QALY 4. INMB: £384 5. 77%
<i>HLA-B*15:02</i> Carbamazepine & phenytoin Epilepsy	1. £60 2. 0.0008 3. £75,391/QALY 4. INMB: -£36 5. 0%	1. £110 2. 0.0008 3. £137,891/QALY 4. INMB: -£86		Excluded from optimised panel - not cost effective, even as incidental finding
<i>HLA-B*57:01</i> Abacavir HIV	1. -£3,148 2. 0.0170 3. Dominant* 4. INMB: £3,658 5. 100%	1. -£3,098 2. 0.0170 3. Dominant* 4. INMB: £3,608	1. -£3,098 2. 0.0170 3. Dominant* 4. INMB: 3,608 5. 100%	1. -£3,098 2. 0.0170 3. Dominant* 4. INMB: £3,608 5. 100%
<i>HLA-B*58:01</i> Allopurinol Gout	1. £49 2. 0.0023 3. £21,491/QALY 4. INMB: £20 5. 65%	1. £99 2. 0.0023 3. £43,230/QALY 4. INMB: -£30	1. £99 2. 0.0023 3. £43,038/QALY 4. INMB: -£30 5. 26%	1. £99 2. 0.023 3. £43,037/QALY 4. INMB: -£30 5. 26%
<i>HLA-B & HLA-DQB1</i> Clozapine Schizophrenia	1. -£623 2. -0.0003 3. £2,273,246/QALY‡ 4. INMB: £615 5. 100%	1. -£573 2. -0.0003 3. £2,090,746/QALY‡ 4. INMB: £565	1. -£573 2. -0.0003 3. £2,126,100/QALY‡ 4. INMB: £565 5. 100%	1. -£573 2. -0.0003 3. £2,117,942/QALY‡ 4. INMB: £565 5. 100%

1. Incremental cost versus no testing
2. Incremental QALYs versus no testing
3. Incremental cost-effectiveness ratio versus no testing
4. Incremental net monetary benefit (INMB), based on a threshold of £30,000 per QALY

5. Likelihood of cost-effectiveness at a threshold of £30,000 per QALY

*South-east quadrant of the cost-effectiveness plane – dominant means less costly and more effective than not testing

‡South-west quadrant of the cost-effectiveness plane – less costly and less effective than not testing (cost-effective if >£30,000 per QALY)

Table 2: Multi-gene panel test result, independent of presenting indication

Scenario	Test cost	Panel cost (95% CR)	Panel QALY (95% CR)	Panel ICER (% viable simulations*)	Implementation
Cost-effectiveness of pre-specified panel	£50	-£378 (-£472, -£284)	0.0069 (0.0023, 0.0117)	Dominant N/A	Dominant at £30,000 per QALY: All results assumed to be actioned
Optimising the cost-effectiveness of the panel (based on £30,000 per QALY threshold)	£50	-£1,388 (-£2619, -£330)	0.0163 (0.0058, 0.0283)	Dominant (100%)	Results for HLA-B*15:02 not reported, and not indicated for patients initially presenting with gout

*Based on the probability of the panel being cost-effective for initial use in at least 2 combinations

‡Dominant means in the south-east quadrant of the cost-effectiveness plane, more effective and less costly

Table 3: Input parameters for estimating cost-utility of multiple-gene test

Allele Drug Condition	Incident prescriptions (per 1000 population)	δ cost for a single- gene test Mean (SD)	Δ QALY for a single- gene test Mean (SD)
<i>HLA-B*57:01</i> Abacavir HIV	0.0940 [32, 33]	£3,148 (£315) ^b [22, 29, 31]	0.0017 (0.0017) ^b [29]
<i>HLA-B*58:01</i> Allopurinol Gout	0.4301 [24, 25]	£49 (£2) ^c [22, 23, 31]	0.0023 (0.0016) ^c [23]
<i>HLA-A*31:01^a</i> Carbamazepine Epilepsy	0.0765 [26]	£268 (£74) ^c [21, 22, 31]	0.0234 (0.0176) ^c [21]
<i>HLA-B*15:02^a</i> Carbamazepine & Phenytoin Epilepsy	0.0765 [22]	£60 ^d (£6) ^b [22, 28, 31]	0.0008 (0.00008) ^b [28]
<i>HLA-B (158T) & HLA-DQB1 (126Q)</i> Clozapine Schizophrenia	0.0370 [33, 34]	£623 (£62) ^b [22, 30, 31]	-0.0003 (0.00003) ^b [30]

^aIn examples where both *HLA-A*31:01* and *HLA-B*15:02* are included on the panel, δ cost and Δ QALY for both genes are combined additively, with a single prevalence in order to reflect the immediate relevance of the incidental find

^bAs no published confidence intervals for incremental costs and QALYs, SD assumed as 10% of the mean

^cStandard deviations taken from original models [21, 23]

^dTest cost not reported so assumed at £50 (\$US65), cost year 2017